The **A**uto**i**mmune **Re**gulator:

AIRE: **Human gene** symbol

Aire: **Mouse**/Rat **gene** symbol

AIRE: **Protein** symbol

AIRE and *Aire*

A Story About Autoimmunity, APECED and Immunology

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Some Historical Highlights

Different authors contributed to the concept of immunological tolerance. From **Paul Ehrlich** ("Horror autotoxicus", 1905) to **Ray Owen** ("dizygotic cattle twins", 1953), **Peter Brian Medawar** (1953), **Frank M, Burnet** (1953) and **Avrion Mitchinson** (1964), between many others who discovered and described several evidences of immunological tolerance.

Until very recently, molecular mechanisms of central tolerance to peripheral antigens has been poorly understood.

AIRE

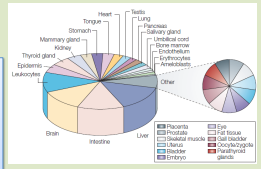
Aire

APECED

1998

Promiscuous Gene Expression in the thymus

Douglas Hanahan (1998) and **Ricardo Pujol-Borell (1998),** both independently, studied and described this phenomenum. They termed it **"Promiscuous Gene Expression",** pointing out an explanation for the role of the thymus in central tolerance to peripheral antigens



Diverse tissues are represented by promiscuous gene expression in medullary thymic epithelial cells

From: Kyewski B and Derbinski J. Nat Rev Immunol. 2004 Sep;4(9):688-98.

2001

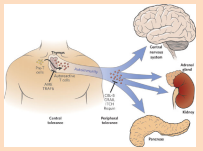
Not long after, numerous authors contributed to the explosion of knowledge in the field.

Among them, **Bruno Kyewski**'s work outstands in the synthesis about the recently elucidated paradigma of the central tolerance (2001).

2002-2013

Several findings in AIRE were reported.

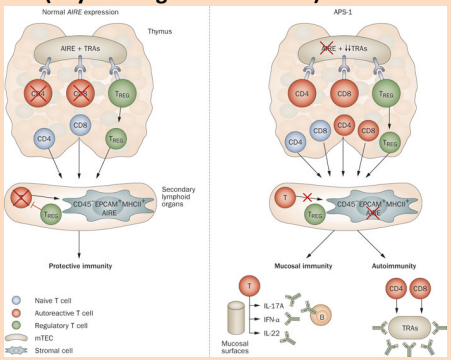
i.e.: **AIRE functions as an E3 ubiquitin ligase.** Daisuke Uchida *et al*. (2004)



From: Bhoj VG and Chen ZJ. Nature. 2009 Mar 26;458(7237):430-7.

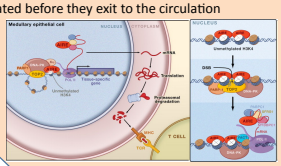
Central tolerance prevents the circulation of self reactive T cells

Central Tolerance explained (Thymic Negative Selection)



From: Akirav EM, *et al*. Nat Rev Endocrinol. 2011 Jan;7(1):25-33.

Because mTEC's express TRA's, autoreactive lymphocytes can be detected and eliminated before they exit to the circulation



From: Kyewski B, Peterson P. Cell.2010 Jan 8;140(1):24-6.

Gene leakage linking

1999

Leaky gene expression in transgenic mice thymus

Persistant "ectopic" **thymic expression** of every "tissue-especific" transgen

Phaenomenum called "leaky gene expression" considered as a recurrent failure of the transgenesis techniques

Back to the thymus

Cloning of *Aire*

Domain profiling

Studies with AIRE protein

Preferent nuclear localization

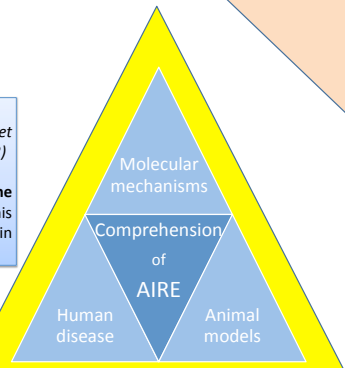
AIRE acts as a transcriptional activator

2002

First two mouse models of APECED. Both knock-out for *Aire* (*Ramsey et al. (2002) and Anderson et al. (2002)*

"AIRE controls promiscuous gene expresion in mTEC's "(Diane Mathis *et al.* 2002). AIRE has a key role in central tolerance

APECED linking



CENTRAL IDEA

The master idea around which the review about AIRE was vertebrated, is very similar to the actual history of its knowledge. Developing an unified concept of AIRE through 3 main sources: (i) information on molecular mechanisms; (ii) information of reported research on associated human disease (APECED); and (iii) animal models of APECED (AIRE KOs).

1997

Isolated a gene responsible for the APECED by *The Finnish –German APECED Consortium* and by Kentaro Nagamine *et al.* (1996)

Gene mapped to **21q22.3** region

Protein product and the gene are named AIRE and *AIRE* respectively, after AutoImmune REgulator

1998

First known gene causative alone of an autoimmune disease

First studies about AIRE

Linking APECED (notable T cell disfunction) to the thymus

AIRE is found to be expressed in the thymus

Estimated prevalence

Iranian Jews → (1: 9000)
Sardinians (Italy) → (1: 14000)
Finns → (1 : 25000)
Slovenians → (1: 43000)
Norwegian → (1: 90000)
Polish → (1: 129000)

Autoimmune Polyglandular Syndrome Type 1 Clinical Features

Disease components	*Percent*
Addison's disease	60–100
Hypoparathyroidism	77–100
Chronic candidiasis	73–100
Ectodermal dysplasia	10–77
Autoimmune thyroid disease	8–18
Type 1 diabetes	4–23
Hypogonadism	31–60
Alopecia	27–72
Vitiligo	4–26
Keratopathy	12–35
Autoimmune hepatitis	10–19
Pernicious anemia	12–15
Chronic gastritis	6

TABLE 1.

Classification of APS

Type	Characteristics
I	Chronic candidiasis, chronic hypoparathyroidism, autoimmune AD (at least 2 present)
II	Autoimmune AD + autoimmune thyroid diseases and/or type 1 DM (AD must always be present)
III	Thyroid autoimmune + other autoimmune diseases (excluding autoimmune AD)
IV	≥ 2 autoimmune diseases (that do not fall in types I, II, or III)

AD = Addison's disease; APS = autoimmune polyendocrine syndrome; DM = diabetes mellitus.

Adapted from Neufeld and Blizzard[1]

From: Schneller C *et al.* Pediatr Ann. 2013 May 1;42(5):203-8.

Prevalence of Autoantibodies in Autoimmune Polyglandular Syndrome Type 1 Patients

Autoantigen	*Prevalence %*
Type1 interferons steroid 21 hydroxylase (P450c21)	100
Side-chain cleavage enzyme (P450scc)	52
Steroid 17 alpha hydroxylase (P450c17)	44
Aromatic L-amino acid decarboxylase (AADC)	51
Glutamic acid decarboxylase (GAD65)	37
Histidine decarboxylase (HDC)	37
Cysteine sulfinic acid decarboxylase (CSAD)	3.6
Tryptophan hydroxylase (TPH)	45
Tyrosine hydroxylase (TH)	44
Thyroglobulin (TG)	36
Thyroid peroxidase (TPO)	36
Transcription factor SOX10	22
Cytochrome P4501A2 (P4501A2)	8
Tyrosine phosphatase-like protein IA-2 (IA-2)	7

Both tables above are extracted from: Weetman AP. Autoimmune disease in endocrinology. New Jersey (USA): Humana Press; 2008. p. 402, 404

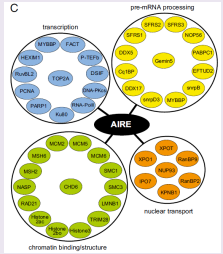
APECED (APS-I) (OMIM 240300)

- Whitaker syndrome
- **A**utoimmune **P**olyglandular **S**yndrome Type 1 (APS1)
- Also known as: **A**utoimmune **P**olyendocrine-**C**andidiasis-**E**ctodermal **D**ystrophy (APECED)

Glosary Box

mTEC = medulary Thymic Epithelial Cell
DC = Dendritic Cell
TRA = Tissue-Restricted Antigen

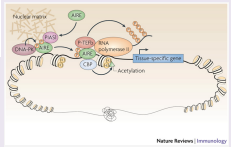
FUTURE CHALLENGES



AIRE interaction evidenced by Co-IP

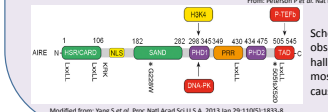
From: Yang S *et al.* Proc Natl Acad Sci U S A. 2013 Jan 29;110(5):1833-8.

- Elucidating etiopathogenesis of APECED and related disorders (*v.g.* vitiligo)
- Role in gametogenesis
- Actual nuclear activity of AIRE
- **Complete molecular mechanisms**
- Antigen processing and TRA presentation
- AIRE and peripheral tolerance
- Non-thymic expression of AIRE



A model for AIRE molecular mechanism

From: Peterson P *et al.* Nat Rev Immunol. 2008 Dec;8(12):948-57.



Schematic model of AIRE, its observed domains, their hallmark interactions, and most common disease-causing mutations

Modified from: Yang S *et al.* Proc Natl Acad Sci U S A. 2013 Jan 29;110(5):1833-8. and Zumer K *et al.* J Immunol. 2013 Mar 15;190(6):2479-82.

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Yang S, Bansal K, Lopes J, Benoist C, Mathis D. Aire's plant homeodomain(PHD)-2 is critical for induction of immunological tolerance. Proc Natl Acad Sci U S A. 2013 Jan 29;110(5):1833-8.

Zumer K, Saksela K, Peterlin BM. The mechanism of tissue-restricted antigen gene expression by AIRE. J Immunol. 2013 Mar 15;190(6):2479-82.

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